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(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	AISSAOUI *et al.*	)	Confirmation No: 9192
Serial No.:	10/555,061	)	Group Art Unit: 1624
Filed:	October 28, 2005	)	Examiner: Murray, Jeffrey H.
For:	QUINOXALIN-3-ONE DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS	)	Docket No.: AC-42-US

MISCELLANEOUS COMMUNICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

The Notice of Allowability was mailed on December 31, 2008, noting that claims 1-5 and 12 have been allowed. The examiner noted that acknowledgment is made of a claim for foreign priority, but the certified copy of the priority document has not been received. Therefore, Applicants enclosed herewith a certified copy of the foreign priority reference, PCT/EP03/04491.

The Examiner is invited to contact the undersigned by telephone in the event of any questions. As this response is filed within three months from the mailing date of the Notice of Allowability, which response is due March 31, 2009, this response is timely.

Respectfully submitted,

Dated: March 27, 2009

By _____
Brittany La
Reg. No. 58,337
HOXIE & ASSOCIATES LLP
75 Main Street, Suite 301
Millburn, NJ 07041
(973) 912-5232

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as **EXPRESS MAIL**, Number: **EH275407306US**, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 27 day of March, 2009.

Patricia Mascenik
Name

Patricia Mascenik
Signature

Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung

Die angehefteten Unterlagen stimmen mit den in den Akten befindlichen Unterlagen der unten bezeichneten europäischen Patentanmeldung überein (Art.2 (3) des Beschlusses der Präsidentin des EPA vom 12.07.2007 (Sonderausgabe Nr. 3, ABl. 2007, J.2.)

Certificate

The attached is a true copy of documents contained in the European patent application indicated below (Art.2(3) of the decision of the President of the EPO of 12.07.2007 (Special edition No. 3, OJ EPO 2007, J.2.)

Attestation

Les documents ci-annexés sont conformes aux documents figurant dans le dossier de la demande de brevet dont le numéro est indiqué ci-dessous (art.2(3) de la décision de la Présidente de l'OEB du 12.07.2007 (Edition spéciale no. 3, JO OEB 2007, J.2.)

Patentanmeldung Nr. **Patent application No.** **Demande de brevet n°**

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München 31

München, den
Munich, 13.03.09

Die Präsidentin des Europäischen Patentamts:
im Auftrag

For the President of the European Patent Office

La Présidente de l'Office européen des Brevets
p.o.

Europäisches Patentamt

European Patent Office

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Bescheinigung

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten internationalen Patentanmeldung überein.

Certificate

The attached documents are exact copies of the international patent application described on the following page, as originally filed

Attestation

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet internationale spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le 16.07.2007

Der Präsident des Europäischen Patentamts, i.A.
For the President of the European Patent Office
Le Président de l'Office européen des brevets, p.o.

TZIKAS Vangeli

Patentanmeldung Nr.
Patent application no. PCT/EP2003/04491
Demande de brevet n°

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldenummer :
Application no. : PCT/EP 2003/04491
Demande n° :

Anmelder : 1. ACTELION PHARMACEUTICALS LTD. - Allschwil, Switzerland
Applicant(s) : 2. AISSAOUI, Hamed - Pulversheim, France (US only)
Demandeur(s) : 3. CLOZEL, Martine - Binningen, Switzerland (US only)
: 4. WELLER, Thomas - Binningen, Switzerland (US only)
: 5. KOBERSTEIN, Ralf - Lörrach, Germany (US only)
: 6. SIFFERLEN, Thierry - Guewenheim, France (US only)
: 7. FISCHLI, Walter - Allschwil, Switzerland (US only)

Bezeichnung der Erfindung :
Title of the invention : NOVEL QUINOXALINONE DERIVATIVES
Titre d'invention :

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Benennung von Vertragsstaaten : Siehe Formblatt PCT/RO/101 (beigefügt)
Designation of contracting states : See Form PCT/RO/101 (enclosed)
Désignation d'états contractants : Voir Formulaire PCT/RO/101 (ci-joint)

PCT REQUEST

Actel 33/OR6

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IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	HOFMANN, Dieter
IV-1-2	Address:	Stratali Therwilerstr. 87 CH-4153 Reinach Switzerland
IV-1-3	Telephone No.	+41 61 713 1560
IV-1-4	Facsimile No.	+41 61 713 15 61
IV-1-5	e-mail	hofmanndrd@bluewin.ch
IV-1-5	Agent's registration No.	25510
V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

ACTELION 33/OR6

Novel Quinoxalinone Derivatives

The present invention relates to novel quinoxalinone derivatives of the general formula I and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I, and especially their use as orexin receptor antagonists.

The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid peptide) (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients (Chemelli R.M. *et al.*, **Cell**, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals. They belong to the superfamily of G-protein coupled receptors (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585): the orexin-1 receptor (OX_1) is selective for OX-A and the orexin-2 receptor (OX_2) is capable to bind OX-A as well as OX-B.

Orexin receptors are found in the mammalian host and may be responsible for many pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcus; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic

hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with deseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardinal infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to orexin.

The present invention provides quinoxalinone derivatives which are non-peptide antagonists of human orexin receptors. In particular, these compounds are of potential use in the treatment of obesity and/or sleep disorders.

International Patent Applications WO099/09024, WO099/58533, WO00/47577, WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin antagonists.

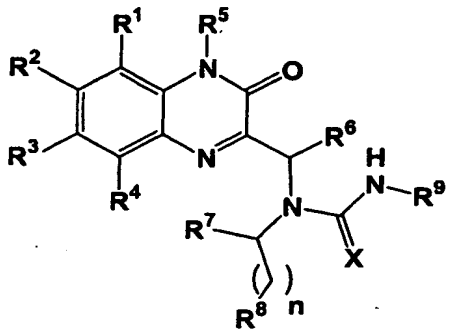
International Patent Applications WO 0251838 discloses tetrahydrobenzazepine derivatives and WO 0168609 discloses tetrahydroisoquinoline derivatives as orexin antagonists

Furthermore, WO 0196302 has been published wherein piperidine derivatives as OX_1 and OX_2 antagonists are disclosed and WO 0185693 has been published wherein N-acyltetrahydroisoquinoline derivatives as selective OX_2 antagonists are disclosed. In addition, WO 0244172 describes morpholine derivatives as antagonists of orexin

receptors. More recently, WO 0290355, WO 0289800, WO 0302559, WO 0302561 describe N-aroyl cyclic amines as orexin antagonists and WO 0244172 describes morpholine derivatives as antagonists of orexin receptors.

The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

The present invention relates to novel quinoxalinone derivatives of the general formula (I).



Formula (I)

wherein:

X is O, S, NH, N-CN;

n is the integer 0, 1, 2, 3;

m is the integer 0, 1, 2, 3;

R^1, R^2, R^3, R^4 independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl-lower alkyloxy, $R^{10}CO$-, CO-$NR^{11}R^{12}$, $R^{11}R^{12}N$-, $R^{10}OOC$-, $R^{10}SO_2NH$-, R^{13}-CO-NH-, or R^2 and R^3 together or R^1 and R^2 together or R^3 and R^4 together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom;

R^5 represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, heterocyclyl-lower alkyl, trifluoromethyl, $-(CH_2)_m$-OH, $-(CH_2)_m$-

O-lower alkyl, -$(CH_2)_m$-CO_2H, -$(CH_2)_m$-CO_2-lower alkyl, -$(CH_2)_m$-$CONH_2$, or -$(CH_2)_m$-CONH-lower alkyl;

R^6 represents hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

R^7 represents hydrogen, aryl, lower alkyl, lower alkenyl, trifluoromethyl, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-CO_2H, -$(CH_2)_m$-CO_2-lower alkyl, -$(CH_2)_m$-$CONH_2$, -$(CH_2)_m$-CONH-lower alkyl, -CON-(lower alkyl)$_2$, -$(CH_2)_m$-N-lower alkyl;

R^8 represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

R^9 represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

R^{10} represents lower alkyl, aryl, aralkyl, heterocyclyl, or heterocyclyl-lower alkyl;

$R^{11}$and R^{12} independently represent hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower-alkyl, aryl, aralkyl, heterocyclyl, or heterocyclyl-lower alkyl;

R^{13} represents lower alkyl, aryl, cycloalkyl, heterocyclyl, $R^{11}R^{12}N$-, or $R^{10}O$-.

The compounds of formula (I) can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

In the present description the term "lower alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-5 carbon atoms. Examples of straight-chain and branched C_1-C_8 alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, tert-butyl and n-pentyl.

The term "lower alkenyl", alone or in combination, signifies a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

The term "lower alkoxy", alone or in combination, signifies a group of the

Formula lower-alkyl-O- in which the term "lower-alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, preferably methoxy and ethoxy.

Lower alkenyloxy groups are preferably vinyloxy and allyloxy.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C_3-C_8 cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl, cyclohexyl or lower alkyl substituted cycloalkyl such as methyl-cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-cyclohexyl, or dimethyl-cyclohexyl.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, nitro, trifluoromethyl, trifluoromethoxy, amino, carboxy, or alkoxycarbonyl such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert-butoxyphenyl, 4-fluorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-naphthyl. Preferred are carboxyphenyl, lower alkoxy-phenyl, hydroxyphenyl and particularly phenyl.

The term "aralkyl", alone or in combination, signifies a lower-alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkoxy or halogen preferably fluorine. Particularly preferred is benzyl.

For the term "heterocyclyl" and "heterocyclyl-lower alkyl", the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or different. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl, cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl,

dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably chlorine and fluorine and particularly fluorine.

The term "carboxy", alone or in combination, signifies a –COOH group.

Preferred compounds are compounds of the general formula I wherein n is the integer 0, 1 or 2, m is the integer of 0, 1 or 2, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meaning given in the formula I above and X represents oxygen.

Examples of preferred compounds are:

3-(2-Ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((S)-1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((R)-1-phenyl-ethyl)-urea.

1-[1-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea.

3-Biphenyl-2-yl-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl-1-(2-methoxy-(S)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

3-(2-Ethoxy-phenyl-1-(2-methoxy-(R)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

N-Methyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

N-Ethyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

N-Cyclopropyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

(R)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.

(S)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.

(3-{1-[3-(Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester.

(2-Oxo-3-{1-[1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-ureido]-ethyl}-2*H*-quinoxalin-1-yl)-acetic acid ethylester.

2-{3-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureidomethyl]-2-oxo-2*H*-quinoxalin-1yl}-acetamide

1-Benzyl-3-(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-urea.

1-Benzyl-3-(2-ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-1-(1-phenyl-ethyl)-urea.

(S)-3-(2-Ethoxy-phenyl)-1-(3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(1-phenyl-ethyl)-urea.

1-(6-Chloro-pyridin-3ylmethyl)-3(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2ylmethyl)-urea.

(S)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

(R)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

N-(2-Ethoxy-phenyl)-*N'*-[1-(-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl)-*N'*-1-phenyl-ethyl-cyanoguanidine.

Examples of physiologically usable or pharmaceutically acceptable salts of the compounds of formula (I) are salts with physiologically compatible mineral acids such as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula (I) with

free acidic groups can also form salts with physiologically compatible bases. Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammoniumsalts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

Preferred compounds as described above have IC_{50} values below 100 nM; which have been determinated with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

The compounds of the general formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity, diabetes, prolactinoma, cardiovascular disorders, cancer, pain, narcolepsy, sleep disorders like insomnia, sleep apnea, parasomnia, depression, anxiety, addictions, schizophrenia, neurodegenerative disorders and dementia.

The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of obesity and sleep disorders.

The compounds of formula (I) may also be used in combination with one or more other therapeutically useful substances e.g. with other orexin receptor antagonists, with lipid lowering agents, with anorectic agents, with sleep inducing agents, with antidepressants or with other drugs beneficial for the prevention or treatment of obesity or sleep disorders.

The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered in enteral or oral form (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the

production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

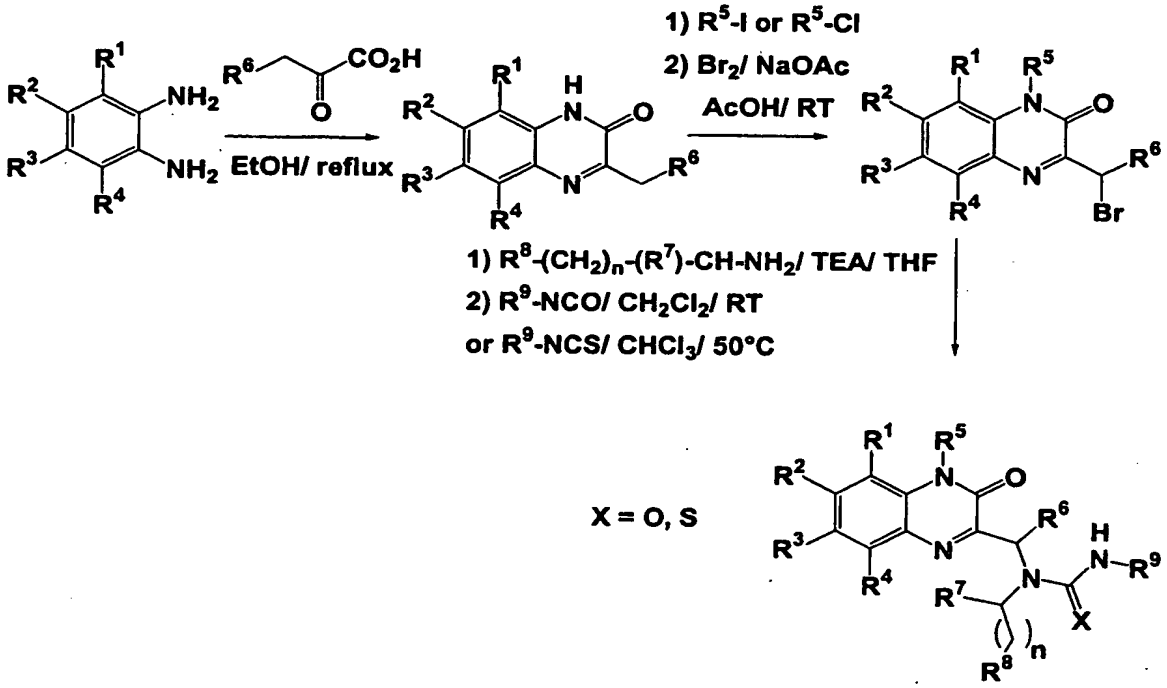
Morever, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The invention also relates to processes for the preparation of compounds of formula (I).

The compounds of general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and R^9 are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atoms may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

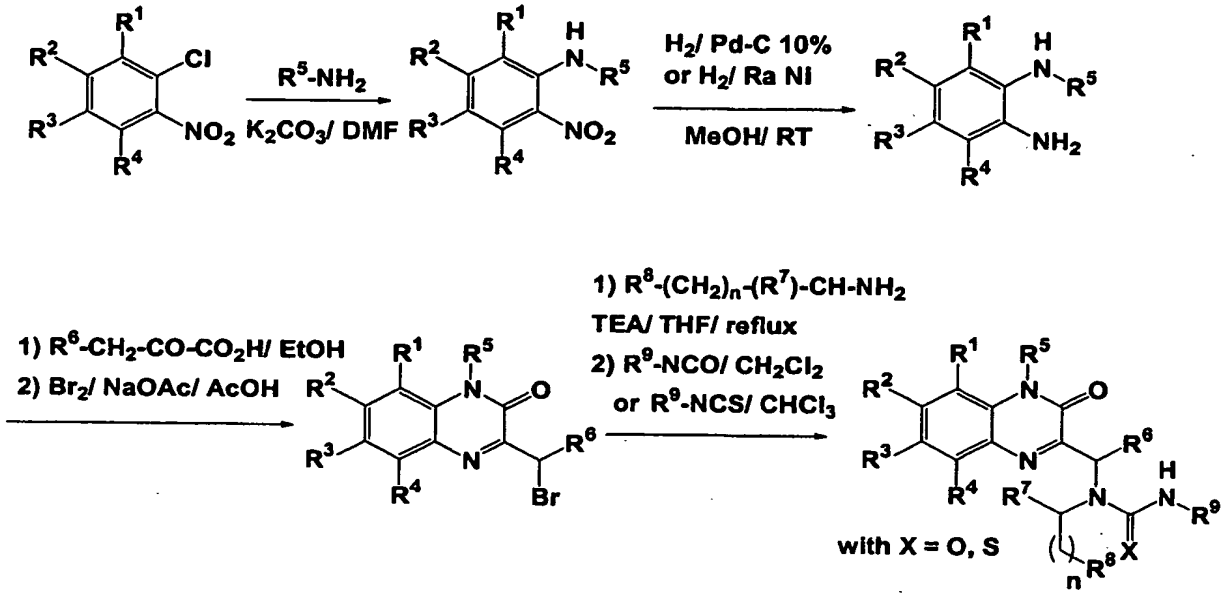
As shown in Scheme 1, the compounds of general formula (I) may be prepared from the corresponding 1,2-phenylenediamine derivatives with the desired 2-oxo carboxylic acid at reflux in EtOH (Lawrence D. S. *et al.*, *J.Med.Chem.* **2001**, 44, 4, 594-601; Bekerman D. G. *et al.*, *Journal of Heterocyclic Chem.* **1992**, 29, 1, 129-133). Subsequent alkylation with R^5-I/ NaOH/ TBAB (Abdel-Ghany H. *et al.*, *Synthetic Communications*, **1990**, 20, 6, 893-900) or with R^5-Cl/ NaOEt/ EtOH (Hermecz I. *et al.*, *Heterocycles* **1998**, 48, 9, 1851-1866) followed by bromination leads to the corresponding bromo intermediate. A second alkylation with the corresponding primary amine yields the secondary amine which is then converted to the desired urea or thiourea compound by reaction with a commercially available or synthetized isocyanate or isothiocyanate (Scheme 1) (March J. *Advanced Organic Chemistry-Reactions, Mechanisms and Structure* **1992**, page 418, 4th edition, John Wiley & Sons).



Scheme 1

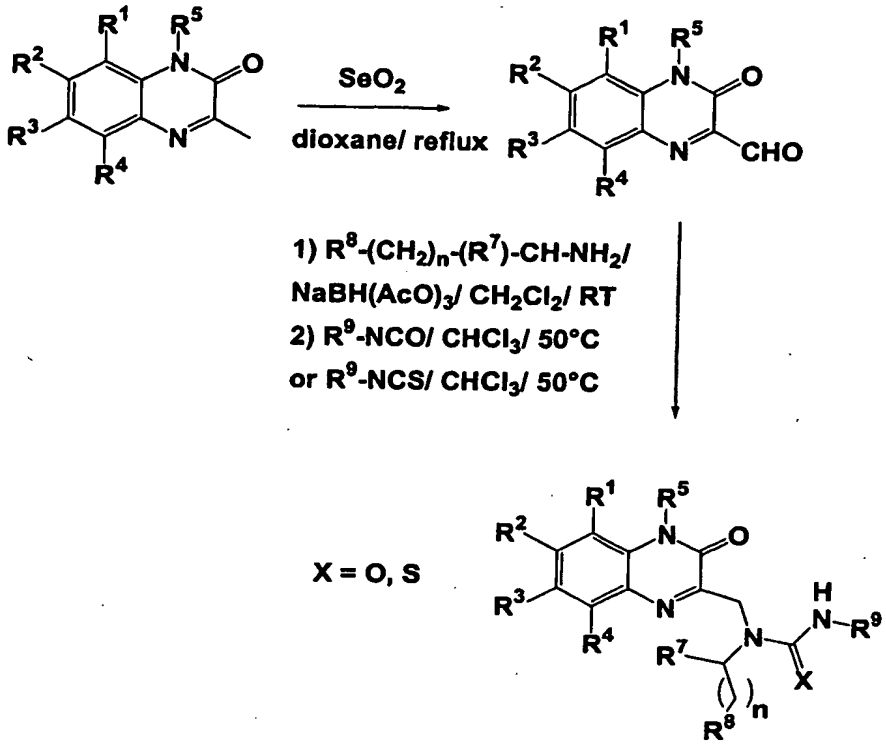
The compounds of general formula (I) may be also prepared from the available 1-chloro-2-nitrobenzene derivative (Scheme 2). Amination under basic conditions followed by the hydrogenation of the resulting nitrobenzene derivative gives the desired aniline intermediate according to the method reported (see Obase H. *et al.*, *J. Heterocyclic Chem.* **1983**, 20, 565-

573). This intermediate is then converted to the corresponding quinoxalinone derivative using the same conditions as described in Scheme 1.



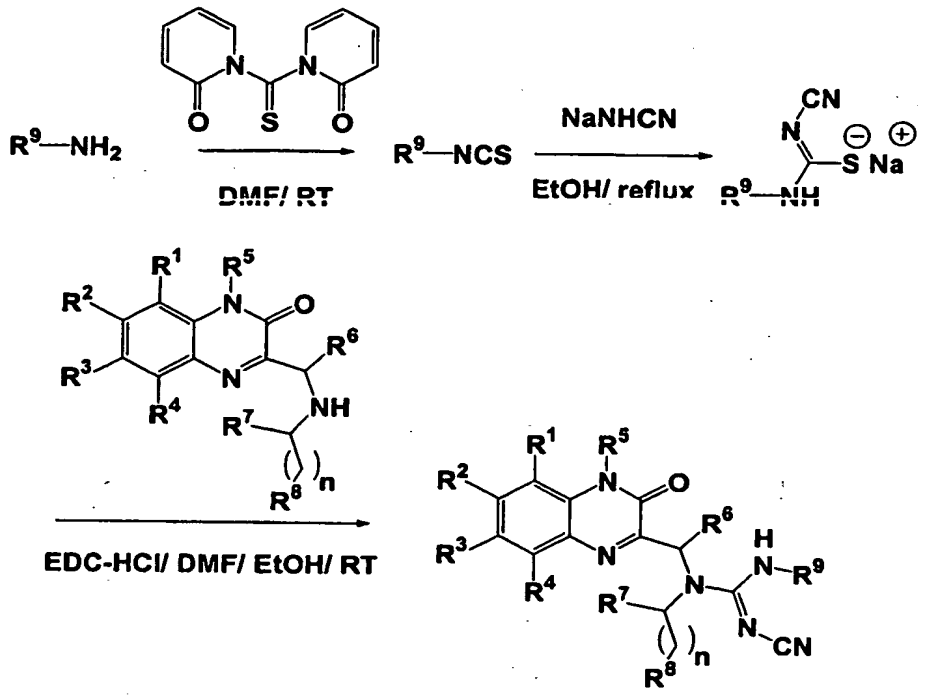
Scheme 2

The compounds of general formula (I) wherein R^6 is hydrogen may also be prepared by reductive amination of the 3-formyl-quinoxalin-2-one derivatives (synthetized by oxidation with selenium dioxide of the corresponding 3-methyl-quinoxalin-2-one derivative: see Ismail M.F. *et al.*, *Ind. J. Chem.* **1981**, 20B, 5, 394-397 and Farghaly A.M. *et al.*, *Farmaco*, **1990**, 45, 4, 431-438) with synthetized or commercially available primary amines (Scheme 3). The resulting secondary amine intermediate is then converted to the desired quinoxalinone derivative using the same conditions as described in Scheme 1.



Scheme 3

The compounds of general formula (I) wherein R^9 is aryl and X is N-CN (cyano-guanidine analogs) may be prepared from synthesized or commercially available isothiocyanate using known methods (see Poindexter G.S. *et al.*, WO 98/ 54136; Atwal K.S. *et al.*, *Tetrahedron Letters,* **1989**, 30, 52, 7313-7316; Atwal K.S. *et al.*, *J. Med. Chem.* **1995**, 38, 1966-1973) (Scheme 4).



Scheme 4

Experimental Section

I. Biology

Determination of OX_1 and OX_2 receptor antagonistic activities

The OX_1 and OX_2 receptor antagonistic activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental method:

Intracellular calcium measurements

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor or the human orexin-2 receptor, were grown in culture medium (Ham F-12 with L-Glutamine) containing 300 µg/ml G418, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % inactivated foetal calf serum (FCS).

The cells were seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which had been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents were from Gibco BRL.

The seeded plates were incubated overnight at 37°C in 5% CO_2.

Human orexin-A as an agonist was prepared as 1 mM stock solution in methanol/ water (1:1), diluted in HBSS containing 0.1 % BSA and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES.

On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) was added to each well.

The 96-well plates were incubated for 60 min at 37° C in 5% CO_2. The loading solution was then aspirated and cells were washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer was left in each well.

Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists were added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by 10 nM orexin-A with buffer in place of antagonist. For each antagonist, IC_{50} value (the concentration of compound needed to inhibit 50 % of the agonistic response) was determined. The IC_{50} values of selected compounds are given in Table 1.

	IC_{50} (nM)	
	OX_1	OX_2
Example 2	15	15
Example 3	15	11
Example 4	40	25
Example 6	5	2
Example 7	43	3
Example 8	53	23
Example 13	6	7
Example 14	14	9

Table 1

II. Chemistry

The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof. All temperatures are stated in °C.

All hydrochloride salts were prepared by dissolving the free base in dichloromethane Followed by treatment with an excess of ethereal HCl (2M).

A. Abbreviations

AcOH	Acetic acid
BSA	Bovine serum albumin
CHO	Chinese hamster ovary
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide

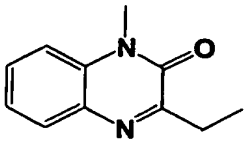
DMSO	Dimethyl sulfoxide
EDC-HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
eq	equivalent
ES	Electron spray
EtOH	Ethanol
FC	Flash chromatography
FCS	Foetal calf serum
FLIPR	Fluorescent imaging plate reader
HBSS	Hank's balanced salt solution
HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
m	multiplet (NMR)
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass spectroscopy
NaOAc	Sodium acetate
NMR	Nuclear magnetic resonance
LC	Liquid chromatography
q	quartet (NMR)
Ra Ni	Raney nickel
R_t	retention time
rt	room temperature
s	singlet (NMR)
t	triplet (NMR)
TBAB	n-Tetrabutylammonium bromide
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

B. 1*H*-quinoxalin-2-one derivatives

1) General procedure:

A mixture of the 1,2-phenylene-diamine derivative (1 g) and the 2-oxo-carboxylic acid derivative (1 eq), in dry EtOH (35 mL) was stirred at reflux for 2 h under nitrogen. After cooling, the EtOH was evaporated to give a crude brown solid. Recrystallisation from EtOH gave the desired quinoxalin-2-one derivative.

a) 3-Ethyl-1-methyl-1*H*-quinoxalin-2-one

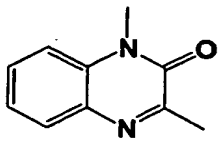


Reaction between *N*-methyl-1,2-phenylene-diamine and 2-oxo-butyric acid gave after recrystallisation (EtOH) 1.2 g (79%) of the title compound;

LC-MS (MeCN/ H_2O: 1/1): R_t =3.81min. *m/z* = 189 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 1.35 (3H, t), 3.0 (2H, q), 3.7 (3H, s), 7.3 (2H, q), 7.5 (1H, t), 7.85 (1H, d).

b) 1,3-Dimethyl-1*H*-quinoxalin-2-one

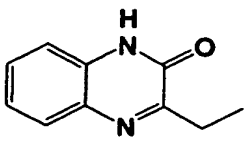


Reaction between *N*-methyl-1,2-phenylene-diamine and pyruvic acid gave after recrystallisation (EtOH) 1.2 g (84%) of the title compound;

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.26 min. *m/z* = 176 (M + 1).

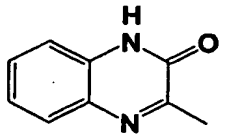
^{1}H-NMR (300MHz; $CDCl_3$) δ 2.6 (3H, s), 3.7 (3H, s), 7.3 (2H, m), 7.55 (1H, t), 7.8 (1H, d).

c) 3-Ethyl-1*H*-quinoxalin-2-one



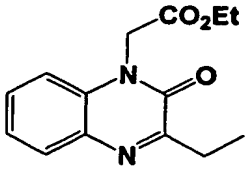
Reaction between 1,2-phenylene-diamine and 2-oxo-butyric acid gave after recrystallisation (EtOH) 0.92 g (57%) of the title compound as a brown solid;
LC-MS (MeCN/ H_2O: 1/1): R_t = 3.36 min. *m/z* = 175 (M + 1).
^{1}H-NMR (300MHz; $CDCl_3$) δ 2.4 (3H, t), 3.1 (2H, q), 7.3 (2H, t), 7.5 (1H, t), 7.85 (1H, d).

d) 3-Methyl-1*H*-quinoxalin-2-one



Reaction between 1,2-phenylene-diamine and pyruvic acid gave after recrystallisation (EtOH) 0.65 g (73%) of the title compound as a beige solid;
LC-MS (MeCN/ H_2O: 1/1): R_t = 2.91 min. *m/z* = 161 (M + 1).
^{1}H-NMR (300MHz; DMSO-d_6) δ 2.4 (3H, s), 7.25 (2H, t), 7.45 (1H, m), 7.85 (1H, d), 12.25 (1H, br.s).

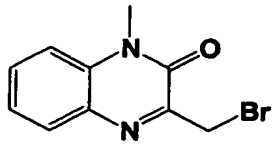
e) (3-Ethyl-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethylester



A mixture of 3-ethyl-1*H*-quinoxalin-2-one (1.6 g), ethyl chloroacetate (1.1 eq), NaOEt (1.1eq) in dry EtOH (15 mL) was stirred at reflux for 16 h under nitrogen. After cooling, the reaction mixture was evaporated in vacuo to dryness, and the residue was dissolved in ether. The resulting solution was washed with saturated $NaHCO_3$ solution, water, dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo to give a crude brown-orange solid.
FC (AcOEt/ heptane: 7/3) gave 1.4 g (43%) of the title compound as a brown solid.
LC-MS (MeCN/ H_2O: 1/1): R_t = 2.91 min. *m/z* = 261 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 1.35 (6H, tt), 3.00 (2H, q), 4.25 (2H, q), 5.00 (2H, s), 7.05 (1H, d), 7.35 (1H, t), 7.55(1H, t), 7.85 (1H, d).

2) 3-Bromomethyl-1-methyl-1*H*-quinoxalin-2-one



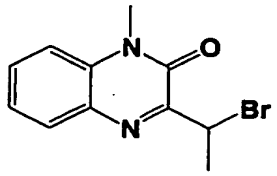
To a mixture of a 1,3-dimethyl-1*H*-quinoxalin-2-one (1g), anhydrous sodium acetate (0.565 g) in glacial AcOH (10 mL) was added dropwise over 10 min. a solution of bromine (0.295 mL) in glacial AcOH (6 mL). The resulting mixture was stirred at rt under nitrogen for 2h; then water and CH_2Cl_2 was added successively. The aqueous layer was extracted once again with CH_2Cl_2, the combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (AcOEt/ heptane: 1/1) gave 0.655 g (45%) of the title compound as a pink-orange solid.

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.91 min. *m/z* = 254 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 3.75 (3H, s), 4.7 (2H, s), 7.35 (2H, m), 7.6 (1H, m), 7.85 (1H, dd).

3) 3-(1-Bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one

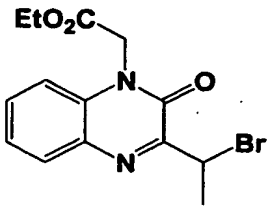


To a mixture of a 3-ethyl-1-methyl-1*H*-quinoxalin-2-one (1g) and anhydrous sodium acetate (0.523 g) in glacial AcOH (10 mL) was added dropwise over 10 min. a solution of bromine (0.273 mL) in glacial AcOH (6 mL). The resulting pale yellow suspension was stirred at rt under nitrogen for 2h, cooled to 0°C, filtered and washed with cold-water to give 1.05 g (73%) of the title compound as a pale yellow solid.

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.91 min. *m/z* = 268 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.1 (3H, t), 3.75 (3H, s), 5.7 (1H, m), 7.35 (2H, m), 7.6 (1H, m), 7.85 (1H, dd).

4) [3-(1-Bromo-ethyl)-2-oxo-2*H*-quinoxalin-1-yl] acetic acid ethyl ester

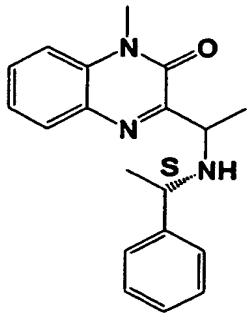


To a mixture of (3-methyl-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethylester (1g), and anhydrous sodium acetate (0.38 g) in glacial AcOH (10 mL) was added dropwise over 10 min. a solution of bromine (0.2 mL) in glacial AcOH (6 mL). The resulting pale yellow suspension was stirred at rt under nitrogen for 2h, combined with water/ CH_2Cl_2, the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue. FC (AcOEt/ n-heptane: 1/1) gave 0.52 g (40%) of the title compound as a beige solid.

LC-MS (MeCN/ H_2O: 1/1): R_t = 2.91 min. *m/z* = 341 (M + 2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 1.25 (3H, t), 2.1 (3H, d), 4.25 (2H, q), 5.9 (1H, d), 6.2 (1H, d), 6.7 (1H, q), 7.1 (1H, d), 7.35 (1H, t), 7.55 (1H, t), 7.9 (1H, d).

5) 1- Methyl-3-[(R,S)-1-((S)-1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one

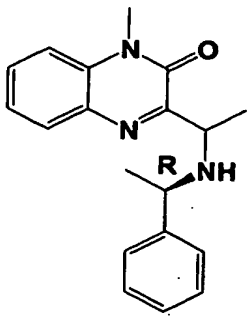


A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (S)-(-)-α-methylbenzyl amine (0.049 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.1 g (86%) of the title compound as a brown-orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.71 min. *m/z* = 308 (M + 1).

6) 1- Methyl-3-[(R,S)-1-((R)-1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one

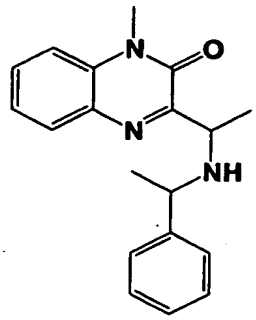


A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(+)-α-methylbenzyl amine (0.049 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2,and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.09 g (75%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.71 min. *m/z* = 308 (M + 1).

7) 1- Methyl-3-[1-(1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one (mixture of diastereoisomers).

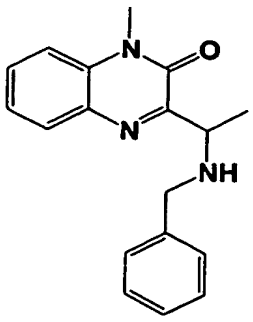


A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), DL (+/-)-α-methylbenzyl amine (0.049 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.09 g (75%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.65 and 0.71 min. *m/z* = 308 (M + 1).

8) 3-(1-Benzylamino-ethyl)-1-methyl-1*H*-quinoxalin-2-one

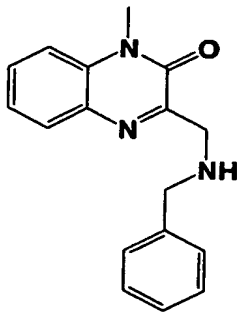


A mixture of 3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), benzylamine (0.041 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.075 g (68%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): $R_t = 0.69$ min. $m/z = 294$ (M + 1).

9) 3-(Benzylamino-methyl)-1-methyl-1*H*-quinoxalin-2-one

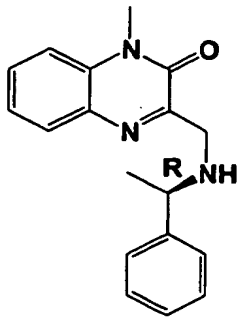


A mixture of 3-bromomethyl-1-methyl-1*H*-quinoxalin-2-one (0.1 g), benzylamine (0.043 mL), and TEA (0.055 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.095 g (86%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): $R_t = 0.71$ min. $m/z = 280$ (M + 1).

10) [R]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one

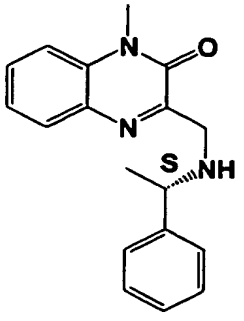


A mixture of 3-bromomethyl-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(+)-α-methylbenzyl amine (0.05 mL), and TEA (0.055 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.095 g (82%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): $R_t = 0.69$ min. $m/z = 294$ (M + 1).

11) [S]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one



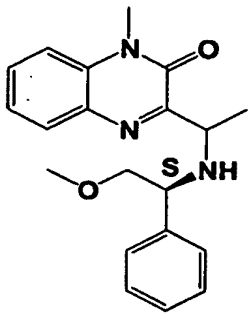
A mixture of 3-bromomethyl-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (S)-(+)-α-methylbenzyl amine (0.05 mL), and TEA (0.055 mL) in dry THF (1 mL) was stirred at

reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.085 g (73%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.69 min. *m/z* = 294 (M + 1).

12) 3-[(R,S)-1-(2-Methoxy-(S)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one

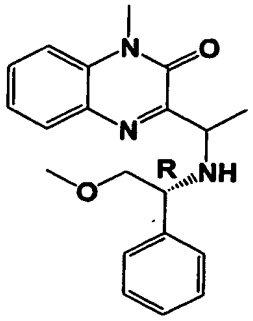


A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (S)-(+)-1-amino-1-phenyl-2-methoxyethane (57 mg, 1eq), and TEA (0.055 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.060 g (47 %) of the title compound as a brown- orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t 2.98 min. *m/z* = 338 (M + 1).

13) 3-[(R,S)-1-(2-Methoxy-(R)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one

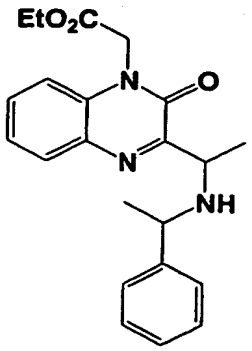


A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(-)-1-amino-1-phenyl-2-methoxyethane (57 mg, 1eq), and TEA (0.055 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.086 g (68 %) of the title compound as a brown- orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t 2.98 min. $m/z = 338$ (M + 1).

14) {2-Oxo-3-[1-(phenyl-ethylamino)-ethyl]-2*H*-quinoxalin-1-yl}-acetic acid ethylester (mixture of diastereoisomers)

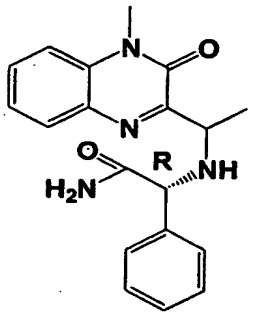


A mixture of [3-(1-bromo-ethyl)-2-oxo-2*H*-quinoxalin-1-yl] acetic acid ethyl ester (0.1 g), (D,L)-(+/-)-α-methylbenzylamine (35.8 mg, 1eq), and TEA (0.041 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.076 g (68 %) of the title compound as a brown- orange viscous oil.

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t 0.76 min. m/z = 380 (M + 1).

15) (R)-2-[(R,S)-1-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethylamino]-2-phenyl-acetamide

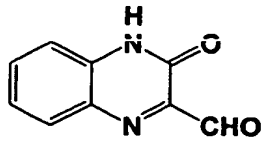


A mixture of 3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(-)-2-phenylglycine amide (57 mg, 1eq), and TEA (0.055 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH_2Cl_2, and the aqueous layer was extracted once again with CH_2Cl_2. The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-orange residue.

FC (CH_2Cl_2/ MeOH: 9/1) gave 0.109 g (87 %) of the title compound as a pale brown viscous oil.

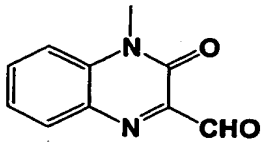
LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t 2.70 min. m/z = 338 (M + 2).

16) **3-Oxo-3,4-dihydro-quinoxaline-2-carbaldehyde**



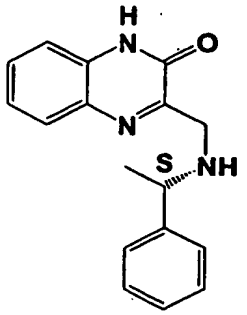
A mixture of 3-methyl-1*H*-quinoxalin-2-one (0.5 g) and selenium dioxide (0.728 g, 2.1 eq) in dry dioxane (33 mL) was stirred at reflux under nitrogen for 30 min. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified by FC (AcOEt) to give 0.44 g (81%) of the title compound as an orange solid. ^{1}H-NMR (300MHz; DMSO-d_6) δ 7.35 (2H, q), 7.7 (1H, t), 7.9 (1H, d), 10.2 (1H, s), 12.8 (1H, br.s).

17) **4-Methyl-3-oxo-3,4-dihydro-quinoxaline-2-carbaldehyde**



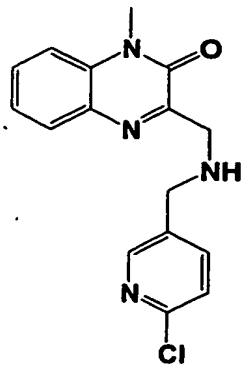
A mixture of 1,3-dimethyl-1*H*-quinoxalin-2-one (1 g) andselenium dioxide (1.33 g, 2.1 eq) in dry dioxane (60 mL) was stirred at reflux under nitrogen for 30 min. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified by FC (AcOEt) to give 0.997 g (92%) of the title compound as a yellow solid. ^{1}H-NMR (300MHz; DMSO-d_6) δ 3.8 (3H, s), 7.35-7.45 (2H, m), 7.7 (1H, t), 8.1(1H, d), 10.5 (1H, s).

18) [S]-3-[(1-Phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one



A mixture of 3-oxo-3,4-dihydro-quinoxaline-2-carbaldehyde (0.1 g), sodium triacetoxyborohydride (0.182 g, 1.5 eq), and (S)-(+)-α-methylbenzyl amine (70 mg) in dry CH_2Cl_2 (1.2 mL) was stirred at rt under nitrogen for 1 day. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified by FC (AcOEt) to give 0.28 g (18%) of the title compound as an orange solid.
LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.66 min. *m/z* = 280 (M + 1).

19) 3-{[(6-Chloro-pyridin-3-ylmethyl)-amino]}-1-methyl-1*H*-quinoxalin-2-one



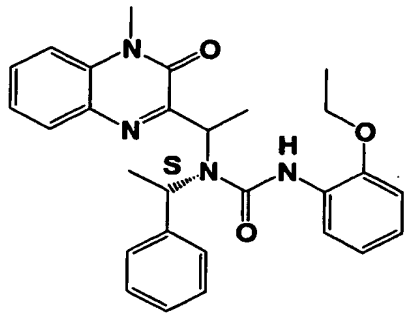
A mixture of 4-methyl-3-oxo-3,4-dihydro-quinoxaline-2-carbaldehyde (0.1 g), sodium triacetoxyborohydride (0.170 g, 1.5 eq), and 2-chloro-5-aminomethylpyridine (0.076 g, 1eq) in dry CH_2Cl_2 (1.5 mL) was stirred at rt under nitrogen for 1 day. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified

by FC (CH_2Cl_2/ MeOH: 9/ 1) to give 0.086 g (51%) of the title compound as an orange oil.

LC-MS (MeCN/ H_2O: 1/1): R_t = 2.93 min. *m/z* = 315 (M + 1).

Example 1

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-(S)- phenyl-ethyl)-urea

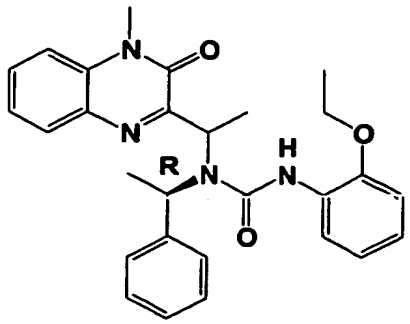


To a solution of 1- Methyl-3-[(R,S)-1-((S)-1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one (50 mg, 0.163 mmol) in dry $CHCl_3$ (1 mL), was added 2-ethoxyphenyl isocyanate (26.3 mg, 0.163 mmol). The resulting reaction mixture was stirred at 50°C under nitrogen for 20h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by FC (CH_2Cl_2/ MeOH: 19/ 1) to give the title compound as a yellow foam (45%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 1.03 min. *m/z* = 471 (M + 1).

Example 2

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((R)-1-phenyl-ethyl)-urea



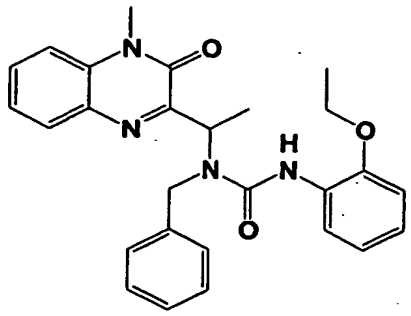
In analogy to Example 1 using the 1- Methyl-3-[(R,S)-1-((R)-1-phenyl-ethylamino)-ethyl]-1H-quinoxalin-2-one (1 eq).

FC (CH_2Cl_2/ MeOH: 19/ 1) afforded the title compound as a yellow oil (48%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 1.03 min. *m/z* = 471 (M + 1).

Example 3

(R,S)-1-Benzyl-3-(2-ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea



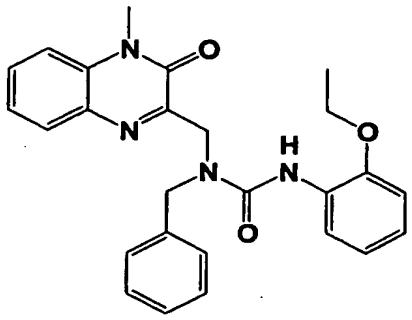
In analogy to Example 1 using the 3-(1-benzylamino-ethyl)-1-methyl-1*H*-quinoxalin-2-one (1 eq).

FC (CH_2Cl_2/ MeOH: 19/ 1) afforded the title compound as a brown-orange oil (43%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 1.01 min. *m/z* = 457 (M + 1).

Example 4

1-Benzyl-3-(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-urea



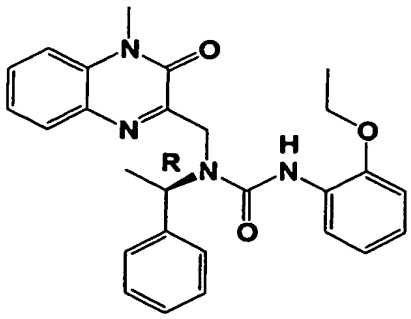
In analogy to Example 1 using the 3-(benzylamino-methyl)-1-methyl-1*H*-quinoxalin-2-one (1 eq).

FC (CH_2Cl_2/ MeOH: 19/ 1) afforded the title compound as an orange oil (57%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.98 min. *m/z* = 443 (M + 1).

Example 5

[R]-3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2ylmethyl)-1-(phenyl-ethyl)-urea



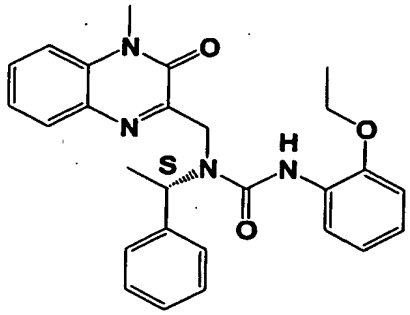
In analogy to Example 1 using the [R]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one (1 eq).

FC (CH_2Cl_2/ MeOH: 19/ 1) afforded the title compound as an orange oil (57%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 1.00 min. *m/z* = 457 (M + 1).

Example 6

[S]-3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2ylmethyl)-1-(phenyl-ethyl)-urea



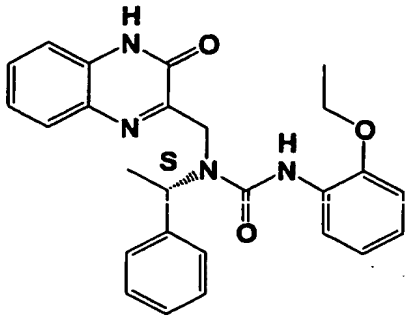
In analogy to Example 1 using the [S]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one (1 eq).

FC (CH_2Cl_2/ MeOH: 19/ 1) afforded the title compound as an orange oil (32%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04%): R_t = 1.00 min. *m/z* = 457 (M + 1).

Example 7

[S]-3-(2-Ethoxy-phenyl)-1-(3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(1-phenyl-ethyl)-urea



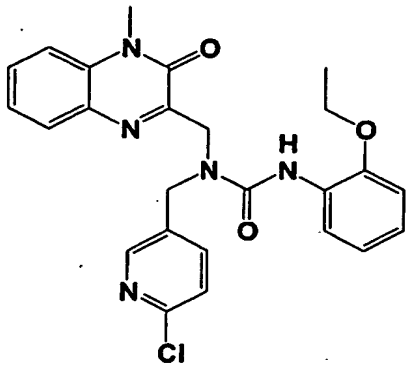
In analogy to Example 1 using the [S]-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one (1 eq)

FC (CH_2Cl_2/ MeOH: 9/ 1) afforded the title compound as a pale-yellow solid (72%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.94 min. *m/z* = 443 (M + 1).

Example 8

1-(6-Chloro-pyridin-3ylmethyl)-3(2-ethoxy-phenyl)-1(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-urea.



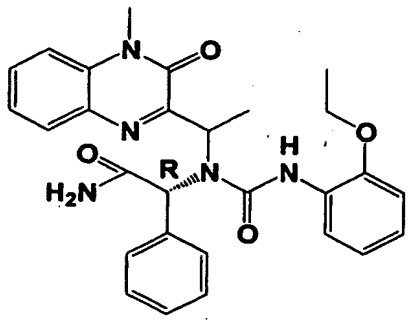
In analogy to Example 1 using the 3-{[(6-chloro-pyridin-3-ylmethyl)-amino]}-1-methyl-1*H*-quinoxalin-2-one (1eq)

FC (CH_2Cl_2/ MeOH: 9/ 1) afforded the title compound as a yellow foam (50%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.86 and 5.41 min. *m/z* = 478 (M + 1).

Example 9

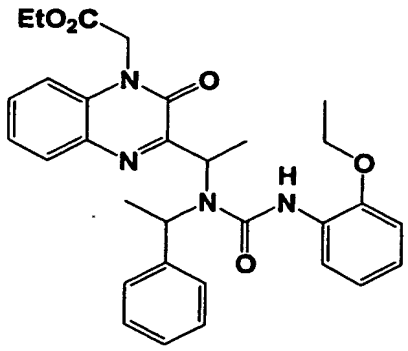
[R]-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.



In analogy to Example 1 using the [R]-2-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethylamino]-2-phenyl-acetamide (1eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as white foam (32%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.63 min. *m/z* = 500 (M + 1).

Example 10

(3-{1-[3-(Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester (mixture of diastereoisomers)



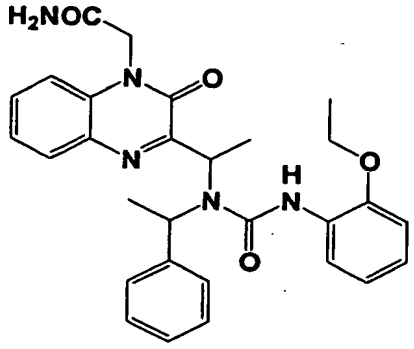
In analogy to Example 1 using the {2-Oxo-3-[1-(phenyl-ethylamino)-ethyl]-2*H*-quinoxalin-1-yl}-acetic acid ethylester (1eq).

FC (AcOEt/ heptane: 3/ 7) afforded the title compound as an orange oil (79%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.95 min. *m/z* = 543 (M + 1).

Example 11

2-{3-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1yl}-acetamide (mixture of diastereoisomers)



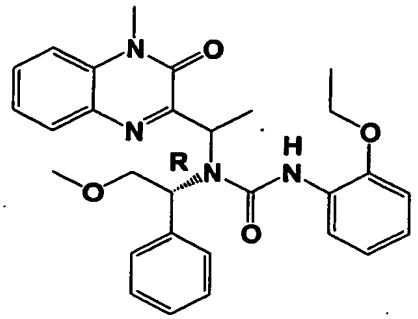
A mixture of (3-{1-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester (0.11 g), and aqueous NaOH 2N (0.5 mL, 5 eq) in a mixture MeOH/ dioxane (4/3) (1.7 mL) was stirred at rt for 20 h. Then the reaction mixture was combined with water/ AcOEt, the aqueous phase was acidified until pH 1-2 with aqueous HCl 2N, and extracted with CH_2Cl_2 (three times). The combined organic extracts were dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo to give the crude acid as a white foam (0.09 g, 85%). To this crude acid (0.05 g) in dry CH_2Cl_2 (1.4 mL), were added successively EDC-HCl (0.026 g, 1eq), DMAP (0.035 g, 3eq), and NH_3 0.5 N in dioxane (0.20 mL, 1eq); the resulting mixture was stirred at rt under nitrogen for 20 h. The mixture was then combined with CH_2Cl_2/ aqueous HCl 2N. The organic layer was washed twice with water, dried (anhydrous $MgSO_4$), filtered and concentrated in vacuo to give a crude oil.

FC (CH_2Cl_2/ MeOH: 9/ 1) afforded the title compound as a beige foam (100%).

LC-MS (MeCN/ H_2O: 1/1 + 0.04% TFA): R_t = 0.91 min. *m/z* = 514 (M +1).

Example 12

3-(2-Ethoxy-phenyl)-1-(2-methoxy-(R)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.



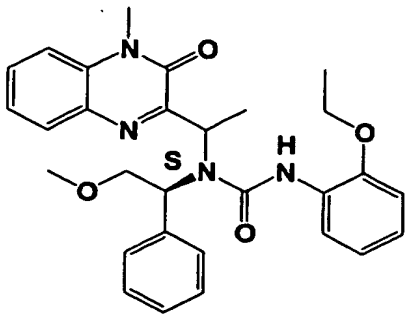
In analogy to Example 1 using the 3-[(R,S)-1-(2-Methoxy-(R)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one (1eq).

FC (AcOEt/ heptane: 1/1) afforded the title compound as a pale brown oil (25%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.27 min. *m/z* = 501 (M + 1).

Example 13

3-(2-Ethoxy-phenyl)-1-(2-methoxy-(S)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.



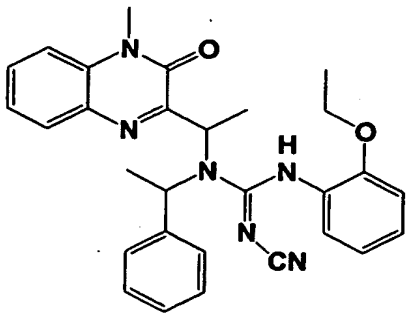
In analogy to Example 1 using the 3-[(R,S)-1-(2-Methoxy-(S)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one (1eq).

FC (AcOEt/ heptane: 1/1) afforded the title compound as a pale brown oil (52%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.28 min. *m/z* = 501 (M + 1).

Example 14

***N*-(2-Ethoxy-phenyl)-*N*-[1-(-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl)-cyanoguanidine (mixture of diastereoismomers)**



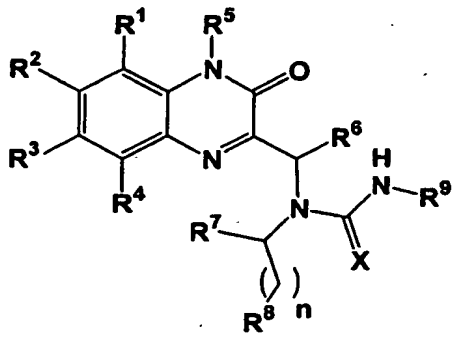
A mixture of 2-ethoxyphenyl isothiocyanate (0.1 g) and sodium hydrogencyanamide (35.71 mg, 1eq) in dry EtOH (2 mL) was stirred at reflux under nitrogen for 3 h. After cooling to rt, EDC-HCl (0. 107 g, 1eq) and a solution of 1- methyl-3-[1-(1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one (0.172 g, 1eq) in dry DMF (1 mL) were added and the resulting mixture reaction was stirred at rt under nitrogen for 20 hours. The mixture was then combined with AcOEt and sat. $NaHCO_3$, the aqueous layer was extracted once again with AcOEt. The combined organic extracts was washed with brine, dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude pale-brown oil.

FC (AcOEt/ n-heptane: 7/3) gave the title compound as a white solid (0.051 g, 18%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.26 min. *m/z* = 495 (M).

Claims

1. Compounds of the general formula (I)



Formula (I)

wherein:

X is O, S, NH, N-CN;

n is the integer 0, 1, 2, 3;

m is the integer 0, 1, 2, 3;

R^1, R^2, R^3, R^4 independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl-lower alkyloxy, $R^{10}CO$-, -CO-N $R^{11}R^{12}$-, $R^{11}R^{12}N$-, $R^{10}OOC$-, $R^{10}SO_2NH$-, R^{13}-CO-NH-, or R^2 and R^3 together or R^1 and R^2 together or R^3 and R^4 together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom;

R^5 represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, heterocyclyl-lower alkyl, trifluoromethyl, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-CO_2H, -$(CH_2)_m$-CO_2-lower alkyl, -$(CH_2)_m$-$CONH_2$, -$(CH_2)_m$-CONH-lower alkyl;

R^6 represents hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^7 represents hydrogen, aryl, lower alkyl, lower alkenyl, trifluoromethyl, -$(CH_2)_m$-OH,

$-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m-CO_2H$, $-(CH_2)_m-CO_2$-lower alkyl, $-(CH_2)_m-CONH_2$, $-(CH_2)_m$-CONH-lower alkyl, -CON-(lower alkyl)$_2$, $-(CH_2)_m$-N-lower alkyl;

R^8 represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^9 represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{10} represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{11}$and R^{12} independently represent hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{13} represents lower alkyl, aryl, cycloalkyl, heterocyclyl, $R^{11}R^{12}N$- or $R^{10}O$-.

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula I, wherein n is the integer 1 or 2, m is the integer 1 or 2, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meaning given in the formula I above and X represents oxygen.

3. Compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 1 or 2, R^5 represents methyl, R^6 represents phenyl, R^1, R^2, R^3, R^4, and R^7 have the meaning given in the formula I above and X represents oxygen.

4. A compound according to any one of claims 1 to 3, selected from the group consisting of

3-(2-Ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((S)-1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((R)-1-phenyl-ethyl)-urea.

1-[1-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea.

3-Biphenyl-2-yl-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl-1-(2-methoxy-(S)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

3-(2-Ethoxy-phenyl-1-(2-methoxy-(R)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

N-Methyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

N-Ethyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

N-Cyclopropyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

(R)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.

(S)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.

(3-{1-[3-(Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester.

(2-Oxo-3-{1-[1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-ureido]-ethyl}-2*H*-quinoxalin-1-yl)-acetic acid ethylester.

2-{3-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureidomethyl]-2-oxo-2*H*-quinoxalin-1yl}-acetamide

1-Benzyl-3-(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-urea.

1-Benzyl-3-(2-ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-1-(1-phenyl-ethyl)-urea.

(S)-3-(2-Ethoxy-phenyl)-1-(3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(1-phenyl-ethyl)-urea.

1-(6-Chloro-pyridin-3ylmethyl)-3(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2ylmethyl)-urea.

(S)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

(R)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

N-(2-Ethoxy-phenyl)-*N'*-[1-(-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl)-*N'*-1-phenyl-ethyl-cyanoguanidine.

5. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, comprising obesity and sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders, containing one or more compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.

6. The compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexin, comprising obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders.

7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

8. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders, containing one or more compounds as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, as active ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.

9. Use of one or more compounds of any one of claims 1 to 4 in combination with other pharmacologically active compounds comprising other orexin receptor antagonists, lipid lowering agents, anorectic agents, sleep inducing agents, antidepressants or other drugs beneficial for the prevention or treatment of disorders given in any one of claims 5 to 8.

10. A compound as described as end-product in any one of examples 1 to 23.

Abstract

The invention relates to novel quinoxalinone derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.